HED DOC. NO. 013505

DATE: **June 2, 1999**

MEMORANDUM

SUBJECT: ***FENTHION*** **- REPLACEMENT OF HUMAN STUDY USED IN RISK ASSESSMENTS -** Report of the Hazard Identification Assessment Review Committee.

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and

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PC Code: 053301

On February 11, 1999, the Health Effect Division's (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the toxicology database for fenthion and selected doses and toxicology endpoints for risk assessment, based solely on **animal toxicity studies**. The HIARC also determined the appropriate uncertainty factors and margins of exposures for dietary and non-dietary risk assessments. **For clarity, transparency, and utility, the decisions made at the previous HIARC meetings along with those made at this meeting are presented in this report. Consequently, the information contained in this report should be used for risk assessments and supersedes all other reports (RfD, TES, HIARC, etc) for fenthion.**

Committee Members in Attendance

Members present were: David Anderson, William Burnam, Virginia Dobozy, Pam Hurley, Mike Ioannou, Tina Levine, Susan Makris, Nicole Paquette, Kathleen Raffaele, Jess Rowland, Brenda Tarplee (Executive Secretary), and Pauline Wagner. Member in absentia: Karen Hamernik

Other HED staff present at the meeting were: John Doherty, Steve Knizner, Alberto Protzel, Margaret Stasikowski, and Ed Zager.

Brenda Tarplee
Executive Secretary
Hazard Identification Assessment Review Committee

I. BACKGROUND

The Health Effects Division's Reference Dose/Peer Review Committee and the Toxicology Endpoints Selection Committee selected doses and endpoints for fenthion from a 28-day study conducted in human subjects for acute and chronic dietary as well as occupational exposure risk assessments. (RfD Document dated 3/11/96, TES Documents dated 1/26/96 and 3/26/96).

On November 18, 1998, at the request of the Division Director, an *ad hoc* group of HED scientists evaluated the animal toxicity studies of fenthion and selected doses and endpoints for dietary and non-dietary risk assessments based *solely* on animal studies *in lieu* of human data. (Report of the *ad hoc* group dated 12/1/98).

In December 10-11, 1998, the Science Advisory Board/Scientific Advisory Panel discussed both the ethical concerns and the scientific merit of using humans subjects for testing pesticides. The Agency is currently developing a policy for the use of human studies in risk assessment. In the interim, HED has taken the following course of action.

In January, 1999, the HIARC developed a specific outline of parameters and questions for the re-examination of human studies. Human studies were used in endpoint selection for risk assessment for eight organophosphates, including fenthion. These studies were re-evaluated according to the parameters and questions developed by the Committee. The HIARC then selected doses and endpoints from toxicity studies with animals for each of these eight organophosphate. The HIARC examined the human data in conjunction with the animal data to determine the appropriate inter-species uncertainty factor.

In the evaluation of the comparative toxicology data in laboratory animals and humans, when the data was suitable for comparison, the Committee relied mainly on the LOAEL for cholinesterase inhibition at comparable time points (duration). The comparative data were evaluated as follows:

> If the comparative data indicate (by the dose level and the magnitude of the effect) that humans are more sensitive than laboratory animals, there is no justification for reducing the 10x inter-species uncertainty factor.
>
> If the comparative data indicate (by the dose level and the magnitude of the effect) that humans and laboratory animals are equally sensitive or that humans are less sensitive than laboratory animals, consideration was given to reducing the inter-species uncertainty factor.

Using the parameters developed for evaluation of the human studies, the HIARC evaluated the 28-day oral study (Griffin, 1979; MRID No. 000147246) with fenthion using human volunteers. The HIARC classified this study as *supplemental* because the results provided useful scientific information that can be used as supportive data along with the results from the animal studies, but the study alone are not sufficient for endpoint selection or risk assessments due to technical limitations.

On February 9, 1999, the HIARC evaluated the doses and toxicology endpoints selected for fenthion based solely on animal toxicity studies. The HIARC also determined the appropriate uncertainty factors and margins of exposures for dietary and non-dietary risk assessments.

For clarity, transparency, and utility, the decisions made at the previous HIARC meetings along with those made at this meeting are presented in this report. Consequently, the information contained in this report should be used for risk assessments.

II. HAZARD IDENTIFICATION

A. Acute Dietary Reference Dose (RfD)

Study Selected: Special Study - Monkeys §None

MRID No. 00147245

Executive Summary: In a monkey study, 4-5 animals/sex were dosed by stomach tube with fenthion (98.1% purity) in corn oil for two years at 0.02, 0.07 and 0.20 mg/kg/day. The general condition of the monkeys was monitored and blood was drawn monthly for plasma and RBC cholinesterase inhibition (ChEI) and assessed by the radiometric method of Michel (MRID No.: 00147245). No inhibition of plasma cholinesterase activity was seen at 0.02 or 0.07 mg/kg/day in either sex at the Week 1 measurement. Plasma ChEI or RBC ChEI was only infrequently noted in the controls. Upon longer exposures, plasma ChEI was frequently inhibited at 0.02 mg/kg/day (maximum 67% in the first six months and especially in females) such that this level was deemed to be a threshold level. Progressively more consistent inhibition was noted at 0.07 and 0.20 mg/kg/day. RBC ChEI was noted to have a threshold for inhibition at 0.07 mg/kg/day (frequent inhibition at this level up to 39% for the first three months of the study). More consistent inhibition was noted at 0.20 mg/kg/day for RBC ChEI. No brain ChEI was noted at study termination and no clinical signs or body weight effects were noted at any dose level. The threshold NOAEL/LOAEL for plasma ChEI was 0.02 mg/kg/day and the LOAEL for RBC ChEI was 0.07 mg/kg/day. The definite NOAEL for plasma ChEI was not established and the NOAEL for RBC ChEI was 0.02 mg/kg/day.

After a careful review of the human and monkey studies it was determined that the monkey study is appropriate for endpoint selection for acute dietary risk assessment. The dose of 0.07 mg/kg/day was recommended as an acute NOAEL for this risk assessment due to lack of plasma or RBC ChEI during the first week of the study.
The LOAEL was 0.2 mg/kg/day for plasma and RBC ChEI. In addition, this NOAEL (in the monkeys) is supported by the marginal (approximately 8%) plasma cholinesterase inhibition seen in humans at 24 hours with no clinical signs or RBC ChEI.

Dose and Endpoint for Risk Assessment: NOAEL=0.07 mg/kg/day was selected based on lack of plasma or RBC ChEI during the first week of the study.

Uncertainty Factor: 30 (10x for intra-species variation and 3x for inter-species extrapolation)

$$\textbf{Acute RfD} = \frac{\text{0.07 mg/kg/day (NOAEL)}}{\text{30 (UF)}} = \textbf{0.002 mg/kg}$$

Comments about Study, Endpoint and UF: **This dose and endpoint replaces the previous dose/endpoint based on the human study.** This dose was considered to be appropriate for acute dietary risk assessment since no plasma cholinesterase inhibition was seen during the first week of the study. In addition, the results of the acute neurotoxicity study in rats (MRID No. 44326401) provided support for this endpoint. In that study plasma (-23%, not significant), RBC (-22% significant), and brain (-9% significant) cholinesterase inhibition were seen at 1.0 mg/kg/day, the lowest dose tested. The acute neurotoxicity study, however, was not selected since ChEI was significantly inhibited only in females; males showed decreases but they did not reach statistical significance.

Conventionally, when a NOAEL from an animal study is selected an UF of 100 is used. However, the HIARC determined that an UF of 30 is adequate for acute risk assessment. The HIARC concluded that the human study is useful only as *supplemental* data. Although this study is classified as supplemental, similar to six other organophosphates, the HIARC determined that the inter-species factor can be reduced for fenthion based on the following reasons: 1) the lack of cholinesterase inhibition 24 hours after dosing in humans and after 7 days of dosing in monkeys; 2) the acute NOAEL (0.07 mg/kg) in monkeys is supported by the marginal (approximately 8%) plasma cholinesterase inhibition (with no clinical signs) at the same dose (0.07 mg/kg)in humans; and 3) the LOAEL (0.02 mg/kg) is the threshold effect level in humans since some statistical significance was seen based on 5-12% plasma cholinesterase inhibition starting at one week of exposure. At 0.07 mg/kg in humans, plasma ChEI reached levels up to 30% after 3 weeks of dosing. In addition, no RBC ChEI, clinical signs, or alterations in clinical chemistry, hematology, or urinalysis were seen at 0.07 or 0.02 mg/kg doses in humans.

Although these data indicated that humans are no more sensitive to acute exposures to fenthion than monkeys, the HIARC determined that a 3x inter-species factor is required. While the human study did provide insight as to when the cholinesterase inhibition is likely to occur, it was not rigorous enough for endpoint selection because it included only 4 male subjects per dose. Additionally, there was concern that brain cholinesterase inhibition (not measurable in humans) could also occur at doses causing plasma cholinesterase inhibition since this has been demonstrated in rats (acute and subchronic neurotoxicity studies).

B. Chronic DietaryRfD

Study Selected: Special Study - Monkeys §None

MRID No. 00147245

Executive Summary: See Acute Dietary

Dose and Endpoint for Risk Assessment: Threshold NOAEL/LOAEL=0.02 mg/kg/day was selected based on plasma cholinesterase inhibition.

Uncertainty Factor: 300 (10x for intra-species variation, 10x for inter-species extrapolation, and 3x for the lack of a defenite NOAEL)

$$\textbf{Chronic RfD} = \frac{0.02 \text{ mg/kg/day (NOAEL)}}{300 \text{ (UF)}} = \textbf{0.00007 mg/kg/day}$$

Comments about Study, Endpoint and UF: **This dose and endpoint replaces the previous dose/endpoint based on the human study.** This dose was considered to be threshold NOAEL/LOAEL because plasma ChEI was frequently inhibited at 0.02 mg/kg/day (maximum 67% in the first six months and especially in females). Progressively more consistent inhibition was noted at 0.07 and 0.20 mg/kg/day. RBC ChEI was noted to have a threshold for inhibition at 0.07 mg/kg/day (frequent inhibition at this level up to 39% for the first three months of the study). More consistent inhibition was noted at 0.20 mg/kg/day for RBC ChEI. No brain ChEI was noted and no clinical signs or body weight effects were noted at any dose level.

The HIARC concluded that the 10x inter-species factor cannot be modified/altered. The study in humans is useful only as *supplemental* data. Although this study provided supportive scientific data, it is not appropriate for use in risk assessment since it included only 4 humans per dose and the treatment regimen (28-days) is not adequate to characterize lifetime exposure. Unlike for acute exposure, relative sensitivity of humans following chronic exposure could not be ascertained due to the lack of long-term data in humans (i.e., 28 day exposure in humans and 1-year exposure in monkey). In addition, there is concern for the occurrence of brain cholinesterase inhibition (not measurable in humans) at the same levels as plasma cholinesterase inhibition in animals as demonstrated in subchronic and chronic studies with rats.

C. Occupational Exposure

1. Dermal Absorption

A dermal absorption factor of 20% was estimated based on the ratio of the LOAEL of 1 mg/kg/day in the oral developmental and the LOAEL of 5 mg/kg/day in the 21-day dermal toxicity studies in the same species (rabbits) based on a

common endpoint (cholinesterase inhibition).

2. Short-Term Dermal

Study Selected: Special Study - Monkeys §None

MRID No. 00147245

Executive Summary: See Acute Dietary

Dose and Endpoint for Risk Assessment: Threshold NOAEL/LOAEL 0.07mg/kg/day was selected based on lack of plasma cholinesterase inhibition.

This dose and endpoint replaces the previous dose/endpoint based on the human study. This dose was considered to be appropriate for short-term dermal risk assessment since no plasma cholinesterase inhibition was seen during the first week of the study.

The HIARC concluded that the human study is useful only as *supplemental* data. Although this study is classified as supplemental, similar to the other six organophosphates, the HIARC determined that the conventional MOE of 100 can be reduced based on the following reasons: 1) the lack of cholinesterase inhibition 24 hours after dosing in humans and after 7 days of dosing in monkeys (this exposure period of concern; 2) the acute NOAEL (0.07 mg/kg) in monkeys is supported by the marginal (approximately 8%) plasma cholinesterase inhibition at the same dose in humans; and 3) the LOAEL (0.02 mg/kg) is the threshold effect level in humans since some statistical significance was seen based on 5-12% plasma cholinesterase inhibition starting at one week of exposure. At 0.07 mg/kg in humans, plasma ChEI reached levels up to 30% after only 3 weeks of dosing. Also, no RBC ChEI, clinical signs or alterations in clinical chemistry, hematology or urinalysis were seen at 0.07 or 0.02 mg/kg doses in humans.

Although these data indicated that humans are no more sensitive only to acute exposures to fenthion than animals, the HIARC determined that a MOE of 30 is required. While the human study did provide insight as to when the cholinesterase inhibition is likely to occur, it was not rigorous enough for endpoint selection because it included only 4 male subjects per dose. Additionally, there was concern that brain cholinesterase inhibition (not measurable in humans) could also occur at doses causing plasma cholinesterase inhibition since this has been demonstrated in rats (acute and subchronic neurotoxicity studies).

Since an oral value was selected a dermal absorption factor of 20% should be used for route-to-route extrapolation.

This risk assessment is required.

3. Intermediate-Term Dermal

Study Selected: Special Study - Monkeys §None

MRID No. 00147245

Executive Summary: See Acute Dietary

Dose and Endpoint for Risk Assessment: Threshold NOAEL/LOAEL=0.02 mg/kg/day was selected based on plasma cholinesterase inhibition.

Comments about Study/Endpoint/MOE: **This dose and endpoint replaces the previous dose/endpoint based on the human study.** The HIARC concluded that the conventional MOE of 100 can not modified/altered. The study in humans is useful only as *supplemental* data. Although this study provided supportive scientific data, it is not appropriate for use in risk assessment since it included only 4 humans per dose and the treatment regimen (28-days) is not adequate for this exposure period of concern (7 to 90 days). In addition, there is concern for the occurrence of brain cholinesterase inhibition (not measurable in humans) at the same level (1.63 mg/kg/day) as plasma cholinesterase inhibition in animals as demonstrated in the 90-day subchronic neurotoxicity study in rats (MRID No. 44339401).

For this risk assessment a MOE of 300 (conventional 100 plus 3x for lack of a defenite NOAEL in the critical study).

Since an oral value was selected a dermal absorption factor of 20% should be used for route-to-route extrapolation.

This risk assessment is required.

4. Long-Term Dermal

Study Selected: Special Study - Monkeys §None

MRID No. 00147245

Executive Summary: See Acute Dietary

Dose and Endpoint for Risk Assessment: Threshold NOAEL/LOAEL=0.02 mg/kg/day was selected based on plasma cholinesterase inhibition.

Comments about Study/Endpoint/MOE: **This dose and endpoint replaces the previous dose/endpoint based on the human study.** The HIARC concluded that the study in humans is useful only as *supplemental* data. Although this study provided supportive scientific data, it is not appropriate for use in risk assessment since it included only 4 humans and the treatment regimen (28-days) is not

adequate to characterize lifetime exposure. Unlike for acute exposure, relative sensitivity of humans following chronic exposure could not be ascertained due to the lack of comparative timer period data (i.e., 28 day exposure in humans and 1-year exposure in monkey). In addition, there is concern for the occurrence of brain cholinesterase (not measurable in humans) at the same levels as plasma cholinesterase inhibition in animals as demonstrated in subchronic and chronic studies.

For this risk assessment a MOE of 300 conventional 100 plus 3x for the lack of a defenite NOAEL in the critical study).

Since an oral value was selected a dermal absorption factor of 20% should be used for route-to-route extrapolation.

This risk assessment is required.

5. Inhalation Exposure (Any Time Period)

Except for an acute inhalation toxicity study, there are no other inhalation toxicity studies available in the data base. Therefore, the oral values should be used for inhalation exposure risk assessments; the route-to-route extrapolation should be as follows

Step I. Convert the inhalation exposure component (i.e., µg a.i/day) using a 100% absorption rate (default value) and an application rate to an **equivalent oral dose** (mg/kg/day).

Step II. Convert the dermal exposure component (i.e., mg/kg/day) using a 20% dermal absorption rate and an application rate to an **equivalent oral dose** (mg/kg/day).

Step II Combine the oral equivalent doses (steps I and II) to obtain a total dose and compare the total oral equivalent dose to calculate the MOEs:

Short-term exposure = 0.07 mg/kg.
Intermediate-and Long term exposure = 0.02 mg/kg/day

D. Margin of Exposure for Occupational/Exposures

A MOE of 30 is required for Short-term dermal and inhalation and a MOE of 300 (conventional 100 plus 3x for the lack of a defenite NOAEL in the critical study) is required for Intermediate and Long-term occupational exposures. There are no registered residential uses at the present time.

E. Aggregate Exposure (Food + Water + Residential) Risk Assessments

Since there are no registered residential uses, aggregate exposure risk assessments will be limited to food plus water.

For **acute** aggregate exposure risk assessment, combine the **high end** exposure values from food plus water and compare it to the acute RfD.

For **chronic** aggregate exposure risk assessment, combine the **average end** exposure values from food plus water and compare it to the chronic RfD.

III. FQPA ASSESSMENT

The FQPA Safety Factor Committee met on June 15 and 16, 1998 to evaluate the hazard and exposure data for fenthion and recommend application of the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996), to ensure the protection of infants and children from exposure to these pesticides.

The FQPA Safety Factor Committee has determined that the 10x FQPA safety factor can be removed. For details, refer to the FQPA Safety Committee Report dated August 6, 1998.

IV. ACUTE TOXICITY

Study	Results	Toxicity Category
81-1. Acute Oral-rats. MRID No.: 40186704.	LD_{50} = 405 (302-681) mg/kg, males = 586 (461-791) mg/kg females	II
81-2. Acute Dermal - rabbits. MRID No.:40186705.	LD_{50} = 963 (744-1162) mg/kg for both sexes combined	II
81-3. Acute Inhalation - rats. MRID No.: 40186706	LC_{50} = 0.507 (0.409 - 0.695) mg/l, males = 0.454 (0.349- 0.658) mg/l, females Deaths in females and tremors and ataxia (both sexes) at lowest doses (0.209 mg/L).	II
81-4. Primary Ocular Irritation - rabbits. MRID No.: 40186708	No cornea or iris irritation was noted. Discharge, redness and swelling were noted in the conjunctiva in all rabbits that was reversed after two days.	III
81-5. Primary Dermal Irritation - rabbits. MRID No.: 40186709	PII = 0	IV
81-6. Dermal Sensitization - guinea pigs. MRID No.: 40186710	Not a sensitizer in the Magnusson-Kligman maximization study	NA--
81-7. Delayed type neurotoxicity-hens. MRID No.: 40229201	No evidence of delayed type neurotoxicity following oral (40 mg/kg > acute LD_{50} or dermal (200 mg/kg).	NA--
81-8. Acute Neurotoxicity - rats MRID No.: 44326401	NOAEL for cholinesterase inhibtion <1 mg/kg/day (LDT) in both sexes.	NA--

V. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

EXPOSURE PERIOD	DOSE/UF	END POINT	STUDY	MOE
Acute Dietary	NOAEL = 0.07 mg/kg	Lack of plasma cholinesterase inhibition at week 1 measurement	Chronic-Monkey	Not Relevant
	UF = 30	**Acute RfD = 0.002 mg/kg**		
Chronic Dietary	NOAEL = 0.02 mg/kg/day	Plasma cholinesterase inhibition	Chronic-Monkey	Not Relevant
	UF = 300	**Chronic RfD = 0.00007 mg/kg/day**		
Dermal Absorption	20% estimated based on the oral LOAEL of 1 mg/kg/day in the oral developmental toxicity study and the dermal LOAEL of 5 mg/kg/day in the 21-day dermal toxicity study in rabbits based on a common endpoint (cholinesterase inhibition)			
Short-Term (Dermal & Inhalation) [a]	Oral NOAEL = 0.07 mg/kg/day	Lack of plasma cholinesterase inhibition at week 1 measurement	Chronic-Monkey	30 [b]
Intermediate-Term (Dermal & Inhalation)[a]	Threshold NOAEL/LOAEL 0.02 mg/kg/day	Plasma cholinesterase inhibition	Chronic-Monkey	300 [c]
Long-Term (Dermal & Inhalation)[a]	Threshold NOAEL/LOAEL 0.02 mg/kg/day	Plasma cholinesterase inhibition	Chronic-Monkey	300 [c]

a = Oral values were selected, therefore route-to-route extrapolation must be used (20%, dermal absorption)

b= MOE of 30 since the inter-species factor was reduced.

c= MOE of 300 due to the lack of a defenite NOAEL in the critical study.

Note: MOEs are for occupational exposure risk assessments; there are no registered residential uses